Complete Summary

GUIDELINE TITLE

Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer.

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Vincent M, Bramwell V, Moran LA, Anderson D. Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 19 p. (Practice guideline; no. 12-6). [27 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Non-leukemic cancers
- Toxic effects of chemotherapy, such as hematologic toxicity, neurotoxicity, ototoxicity, and nephrotoxicity

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the safety and effectiveness of amifostine to ameliorate the clinically important side effects of chemotherapy in patients with solid tumours, with acceptable toxicity and no significant degree of tumour protection
- To evaluate if amifostine, when added to chemotherapy in patients with solid tumours, results in a meaningful increase in survival and/or an improvement in quality of life, over and above what can be achieved by alternative strategies such as dose reduction of the chemotherapy or drug substitution

TARGET POPULATION

Patients with non-leukemic cancers (i.e., solid tumors) receiving conventional doses of alkylating agents and/or moderate or higher doses of cisplatin

INTERVENTIONS AND PRACTICES CONSIDERED

Use of amifostine to ameliorate the toxic effect of chemotherapy

MAJOR OUTCOMES CONSIDERED

- Primary clinical outcomes are those that reflect the toxic effects of chemotherapy: hematological toxicities or myelosuppression, neurotoxicity (including ototoxicity) and nephrotoxicity
- Secondary outcomes include survival, tumour response and quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

1998 Guideline
The MEDLINE (1966 to June 1998) and CANCERLIT (1983 to June 1998) databases were searched using the medical subject heading (MeSH) terms: amifostine, neoplasms, double-blind method, single-blind method, placebos, and random (truncated); and the text words: amifostine, WR-2721, cancer, tumour (or tumor), and random (truncated). The search also included the publication types: practice guideline, meta-analysis and randomized controlled trial. The Physician Data Query (PDQ) database and the Proceedings of the Annual Meeting of the American Society of Clinical Oncology (ASCO) (1995 to 1998) were searched for reports of newly completed or ongoing trials. The search was originally performed in December 1997 for the evidence-based recommendation,

and was updated in June 1998 for the final version of this practice guideline. Articles identified by the searches or cited in the relevant papers were retrieved and reviewed, and the reference lists of relevant articles were scanned for additional studies.

2003 Update

The original literature search was updated using MEDLINE (through October 2002), CANCERLIT (through October 2002), the Cochrane Library (through Issue 3 2002) and the 1995-2002 proceedings of the annual meeting of the American Society of Clinical Oncology.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials comparing amifostine with placebo or observation in patients receiving chemotherapy for solid tumours.
2. Trials measuring hematological toxicity, nephrotoxicity, neurotoxicity or ototoxicity.
3. Phase II trials were included if patients were randomly allocated to treatment groups.
4. Abstracts of trials were considered.

Exclusion Criteria

1. Trials of amifostine in bone marrow transplantation or radiotherapy were excluded.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

1998 Guideline

Five randomized controlled trials (RCTs) were identified that met the inclusion criteria.

2003 Update

One practice guideline and eight randomized controlled trials were located in literature update searches.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

1998 Guideline

The trials of amifostine employed a variety of treatment regimens in different disease settings, and examined the effect of amifostine on a range of toxic effects of several chemotherapeutic agents. Due to the inconsistency in reporting outcomes, as well as other important differences among the trials, it was judged inappropriate to pool the data by performing a meta-analysis.

2003 Update

The information pertaining to the 1998 guideline, listed above, remains current.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

1998 Guideline

Members of the Systemic Treatment Disease Site Group (STDSG) focused their discussion of amifostine on the indications for its use and the evidence from randomized controlled trials.

The group acknowledged that, because of the limited number of trials, indications for the use of amifostine are not clear cut. However the greatest potential benefit seems to be in situations where amifostine may protect against the irreversible toxicities of cisplatin (neurotoxicity, nephrotoxicity, ototoxicity). Weighing the costs and potential harms of its use are also important before making a decision to use the drug. The group felt that the recommendation should advise against the use of amifostine with taxanes and mention that there are treatment alternatives to amifostine.

Concerning the evidence from randomized trials of amifostine, STDSG members discussed the small number of studies and the small numbers of patients in each of these studies. Amifostine has shown statistically significant benefits in reducing a number of toxic effects associated with chemotherapy treatment of cancer patients. However, members of the STDSG noted that the studies lacked statistical power to detect differences in response and survival, and thus could not definitely exclude tumor protection. It was agreed that more trials of sufficient size are needed in order to assess these effects, although realistically these may not be done. However, there might, in the future, be the possibility to perform a meta-analysis across multiple trials addressing the issue of tumor protection.

2003 Update

Further data has subsequently been published on the use of amifostine with paclitaxel and this bullet of the recommendation has been modified.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Two economic studies of amifostine have been reported. Dranitsaris conducted a Canadian-situated "willingness to pay" study which arrived at an estimate as to what that the Canadian tax-paying public would be prepared to pay in order to avoid febrile neutropenia. The study used the data from the randomized controlled trial by Kemp, Rose and colleagues, which included the now obsolete cisplatin/cyclophosphamide regimen for ovarian cancer. In his report, Dranitsaris concluded that at the present price of amifostine its use would be cost neutral; respondents stated that they would be willing to pay an extra $3476 Canadian over their lifetimes to avoid febrile neutropenia. The actual cost of amifostine to achieve this is $3826. Net cost is therefore $350 per patient (95% confidence interval is -$850 to +$1551). Importantly, this study indicated that a lower dose of 740 mg/m^2 amifostine would be a better buy than granulocyte colony-stimulating factor (G-CSF). Furthermore, this study did not consider other social benefits such as the avoidance of neurotoxicity, ototoxicity or nephrotoxicity. The methodology of this study is a variant of cost-benefit analysis, and is thought to avoid some pitfalls inherent in cost effectiveness analysis. Methodological controversies are discussed by the author in this publication, together with a justification of his approach, which captured values from all relevant groups (future patients as well as non-users).

Fishman and colleagues conducted a cost-utility analysis based on American cost data. Their study also employed the obsolete cisplatin/cyclophosphamide data from the study by Kemp, Rose and colleagues. They concluded that amifostine is within the range of generally accepted cost-effective therapies for the United States. These data are of marginal relevance in Ontario.

Amifostine retails in Canada at approximately $0.50/mg, or $250 Canadian per 500-mg vial. Based on a dosage rate of 910 mg/m^2, administered once per cycle, for an average individual of 70 kg or 1.7 m^2, amifostine costs about $780 per cycle. At a dose of 740 mg/m^2 per cycle, the cost falls to approximately $640 per cycle. The assumption has been made that the complete contents of the vial are used and not discarded. Carboplatin is currently less expensive than cisplatin overall, with an approximate additional cost per cycle for the platinum component of $122 for 350 mg/m^2 of carboplatin for an average individual of 1.7 m^2. Granulocyte colony-stimulating factor currently costs approximately $2000 per cycle (1 vial/day for 14 days).

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

1998 Guideline
Practitioner feedback was obtained through a mailed survey of 160 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the

draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Systemic Treatment Disease Site Group. The approved practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Systemic Treatment Disease Site Group and the Practice Guidelines Coordinating Committee.

2003 Update
New evidence from review and updating activities has not been subject to external review at this time.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

In the treatment of patients with non-leukemic cancer, with conventional doses of alkylating agents and/or moderate or higher doses of cisplatin, the use of amifostine should be guided by the following considerations:

- In patients scheduled to receive high per cycle doses of cisplatin ($\geq$100 mg/m^2) or high cumulative doses ($\geq$600 mg/m^2), amifostine is a reasonable therapeutic option to reduce the incidence and severity of neurotoxicity, ototoxicity or clinically relevant nephrotoxicity. There are currently no data to determine whether amifostine produces similar benefits at lower per cycle doses or cumulative doses of cisplatin. However, the incidence of neurotoxicity is predicted to rise at cumulative doses of cisplatin ($\geq$300 mg/m^2) and the use of amifostine could be considered in this setting.
- Amifostine is one of several reasonable therapeutic options to reduce myelosuppression. In assessing the effects of amifostine on quality of life, particularly when amifostine is used as part of palliative treatment, acute toxic effects of amifostine, such as nausea and vomiting and hypotension, need to be weighed against its ability (based on one randomized study) to reduce the morbidity of myelosuppression (episodes of neutropenic fever).
- If the objective of treatment with amifostine is to improve survival by means of dose maintenance of chemotherapy, there is no evidence to justify the routine use of amifostine.

Note: Amifostine has been investigated with only a limited number of cytotoxic agents apart from the alkylating agents and platinum analogues. One of these is paclitaxel, for which there is conflicting evidence regarding a pharmacokinetic interaction with amifostine. Evidence from a randomized phase II trial suggests that amifostine does not provide protection from any of the toxicities (including neurotoxicity) of single-agent paclitaxel, despite preclinical evidence that a selective cytoprotective effect for normal cells might exist. This finding is not surprising, given the absence of any plausible biochemical explanation for a protective effect (apart from a pharmacokinetic one) and given the mechanism of action of the taxane. However, the trial indicated no tumour-protective effect either and amifostine should be further investigated as a cytoprotectant in platinum-taxane combinations.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

1998 Guideline

Five randomized controlled trials were identified which evaluated the effects of amifostine on chemotherapy-induced toxicities: 4 compared chemotherapy plus amifostine with chemotherapy alone, and 1 trial compared chemotherapy plus amifostine with chemotherapy plus granulocyte-colony stimulating factor (G-CSF). Four trials used platinum-based regimens in patients with a variety of malignancies, and one trial used mitomycin-C in patients with colorectal adenocarcinoma. Only one trial involved more than 100 patients, and this trial also reported the effects of treatment on neurotoxicity, ototoxicity and nephrotoxicity.

2003 Update

One practice guideline was located in the literature update searches. The guideline, developed by the American Society of Clinical Oncology, was based on the same evidence as the current guideline produced by the Practice Guidelines Initiative (PGI). Appendix 2 of the original guideline document contains a comparison between the PGI guideline and the American Society of Clinical Oncology guideline.

Eight randomized controlled trials that met the eligibility criteria were located in literature update searches. None of these trials were placebo-controlled. These trials have been added to Tables 1 and 2 of the original guideline document. Five trials reported hematologic toxic effects using various outcome measures. Four trials reported on nephrotoxicity outcomes and four trials reported on neurotoxicity outcomes including ototoxicity. Survival and/or tumour response data were available from five trial reports. Quality of life was not assessed in any of the new trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Eight trials showed a trend in favour of amifostine for the protection of bone marrow against the hematologic toxic effects of chemotherapy. One large randomized controlled trial involving ovarian cancer patients receiving cyclophosphamide and cisplatin showed statistically significant differences in favour of the amifostine group in the number of patients experiencing grade 4 neutropenia in course one (10% vs. 21%; p=0.019), in the number of patients failing to recover from grade 4 neutropenia after courses two to four (44% vs. 65%; p=0.004), and in the number of patients discontinuing treatment due to hematologic toxicity (1% vs. 7%; p=0.016). A smaller randomized controlled trial involving breast cancer patients treated with paclitaxel with or without amifostine showed no protective benefits for

amifostine on any measure of hematologic toxicity. Another randomized controlled trial involving patients with small-cell lung cancer receiving ifosfamide, carboplatin and etoposide with or without amifostine showed no benefits for amifostine on any measure of hematologic toxicity. A statistically significant difference in favour of amifostine was noted for both the length of hospital stays and the time on antibiotics in one trial reporting these outcomes.

- Renal toxicity was measured in six trials, and in all six, amifostine use was associated with significantly favourable outcomes on measures of renal toxicity. Amifostine protection against neurotoxicity (including ototoxicity) was reported in two of the four studies that measured neurotoxicity. No difference was detected for survival or tumour response rates in the nine studies reporting these outcomes.

POTENTIAL HARMS

The most concerning side effect of amifostine is hypotension during administration, resulting in discontinuation of amifostine in 25% to 62% of those being treated. Nausea and vomiting occurred more often in the amifostine groups in all four trials reporting this outcome. Other, more mild, side effects included flushing, sneezing, dizziness, hiccups, and chills.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Although the limited number of randomized controlled trials to date indicate no adverse impact of amifostine on tumour response or survival, the lack of a tumour protective effect in all situations should not yet be automatically assumed. Consequently the use of amifostine in the curative or adjuvant setting should preferably take place in the context of a clinical trial.
- There are limited data regarding the potential for interaction between amifostine and some other cytotoxic agents. Use of amifostine with non-platinum non-alkylating cytotoxic agents should preferably take place in the context of a clinical trial.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Vincent M, Bramwell V, Moran LA, Anderson D. Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 19 p. (Practice guideline; no. 12-6). [27 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Dec 18 (updated online 2003 Jan)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group (STDSG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Systemic Treatment Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 14, 2001 and most recently on July 21, 2003. The most recent information was verified by the guideline developer as of August 6, 2003.

COPYRIGHT STATEMENT

Date Modified: 11/15/2004